Impaired cerebral blood flow networks in temporal lobe epilepsy with hippocampal sclerosis: A graph theoretical approach

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ABSTRACT

Graph theory is an emerging method to investigate brain networks. Altered cerebral blood flow (CBF) has frequently been reported in temporal lobe epilepsy (TLE), but graph theoretical findings of CBF are poorly understood. Here, we explored graph theoretical networks of CBF in TLE using arterial spin labeling imaging. We recruited patients with TLE and unilateral hippocampal sclerosis (HS) (19 patients with left TLE, and 21 with right TLE) and 20 gender- and age-matched healthy control subjects. We obtained all participants' CBF maps using pseudo-continuous arterial spin labeling and analyzed them using the Graph Analysis Toolbox (GAT) software program. As a result, compared to the controls, the patients with left TLE showed a significantly low clustering coefficient ($p = 0.024$), local efficiency ($p = 0.001$), global efficiency ($p = 0.010$), and high transitivity ($p = 0.015$), whereas the patients with right TLE showed significantly high assortativity ($p = 0.046$) and transitivity ($p = 0.011$). The group with right TLE also had high characteristic path length values ($p = 0.085$), low global efficiency ($p = 0.078$), and low resilience to targeted attack ($p = 0.101$) at a trend level. Lower normalized clustering coefficient ($p = 0.081$) in the left TLE and higher normalized characteristic path length ($p = 0.089$) in the right TLE were found also at a trend level. Both the patients with left and right TLE showed significantly decreased clustering in similar areas, i.e., the cingulate gyri, precuneus, and occipital lobe. Our findings revealed differing left–right network metrics in which an inefficient CBF network in left TLE and vulnerability to irritation in right TLE are suggested. The left–right common finding of regional decreased clustering might reflect impaired default-mode networks in TLE.

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1. Introduction

Graph theory, an emerging mathematical method for investigating network connections in the brain as a small world [1], is also expected to reveal the network characteristics in the field of epilepsy [2]. An increasing number of studies have been published regarding graph theory and epilepsy using electrophysiological methods [3], diffusion tract imaging [4], or structural imaging [5,6].

In epilepsy, altered cerebral blood flow (CBF) reflecting functional abnormalities of the brain has been extensively reported and applied to the detection of seizure foci [7]. While graph theoretical networks of CBF in individuals with epilepsy have not been well investigated, the corresponding networks in healthy subjects were examined using single photon emission computed tomography (SPECT) [8], in which anatomical covariance methods were applied in common with several other studies about gray matter covariance [9,10]. Several graph theoretical studies with other modalities have revealed brain networks in epilepsy, but further investigations of CBF graph theoretical networks in epilepsy are needed to help address this disorder, its etiology, and its treatment.

Regional CBF can also be evaluated noninvasively by arterial spin labeling imaging [11], and its usefulness in temporal lobe epilepsy (TLE) was also reported [12]. Temporal lobe epilepsy is the most common form of adult focal epilepsy [13], and hippocampal sclerosis (HS) is considered the most frequent and distinct etiology [14]. Our aim in

the present study was to explore graph theoretical networks of CBF in patients with TLE with HS, using arterial spin labeling imaging.

2. Material and methods

2.1. Patients and control subjects

We recruited consecutive patients with TLE and unilateral HS (19 with left HS, 21 with right HS) who were examined at our institute between May 2014 and November 2015. The diagnosis of TLE was based on the presence of simple or complex partial seizures consistent with TLE and focal epileptiform discharge predominantly in a unilateral temporal area as observed by conventional scalp electroencephalography (EEG). The existence of unilateral HS on conventional MRI was diagnosed by a single experienced neuroradiologist (N.S.) based on the following criteria: ipsilateral reduced hippocampal volume, increased T2 signal on the hippocampus, and abnormal morphology (i.e., a loss of internal architecture of the stratum radiatum, a thin layer of white matter that separates the dentate nucleus and Ammon's horn). In addition, we performed automated volumetry of their hippocampi for confirmation of unilateral hippocampal atrophy (see below).

Patients with the following criteria were excluded: a significant medical history of acute encephalitis, meningitis, severe head trauma, or ischemic encephalopathy; suspicious epileptogenic lesions (e.g., tumor, cortical dysplasia, or vascular malformation) on MRI other than ipsilateral HS at the abnormal EEG side; epileptiform discharges in extra-temporal regions on EEG; and those who reported having had a seizure within 24 h prior to the examination.

Of the 40 patients, 11 patients' exams were performed as presurgical evaluation, whereas the others underwent follow-up MRI scans. In all 5 patients who eventually underwent surgery, we verified histopathological HS on the resected tissues.

We also recruited 20 healthy age- and gender-matched subjects as controls. The demographics of all participants are described in Table 1. No significant differences in age and gender among the three groups, and in disease duration and mean number of antiepileptic drugs between the patients' groups were identified. When comparing all the patients to controls, there were no significant differences in age ($p = 0.99$, unpaired t-test) and gender ($p = 0.78$, Pearson's χ^2 test).

All participants gave written informed consent for their data to be used in the study, which was approved by the institutional review board at the National Center of Neurology and Psychiatry Hospital.

2.2. MRI acquisitions and processing: cerebral blood flow

All MRI scans were performed on a 3-T MR system (Philips Medical Systems, Best, The Netherlands), and the pseudo-continuous

arterial spin labeling (pCASL) technique was used. No seizure was observed during any scans. The imaging parameters for the pCASL experiments were single-shot gradient-echo echo planar imaging in combination with parallel imaging (sensitivity encoding [SENSE] factor 2.0), repetition time = 4000 ms, echo time = 12 ms, matrix = 64×64, field of view = 240×240, voxel size = 3.75×3.75 mm, 20 slices acquired in ascending order, slice thickness = 7 mm, 1-mm gap between slices, labeling duration = 1650 ms, postspin labeling delay = 1520 ms, time interval between consecutive slice acquisitions = 32.0 ms, radiofrequency duration = 0.5 ms, pause between radio frequency pulses = 0.5 ms, labeling pulse flip angle = 18°, bandwidth = 3.3 kHz/pixel, and echo train length = 35. Thirty-two pairs of control/label images were acquired and averaged. The scan duration was 4 min and 24 s. For the measurement of the magnetization of arterial blood and also for segmentation purposes, an echo planar imaging M0 image was obtained separately with the same geometry and the same imaging parameters as the pCASL without labeling.

Collected data were analyzed using ASLtbx software working on Matlab (MathWorks, Natick, MA, USA) [15]. The CBF maps were then normalized with the DARTEL (diffeomorphic anatomical registration using the exponentiated lie) registration method [16] using a template made from the average CBF maps of healthy subjects obtained previously at our institute. Each map was then spatially smoothed with a 4-mm full-width at half-maximum Gaussian kernel to decrease spatial noise and compensate for the inexactitude of normalization.

2.3. MRI acquisitions and processing: gray matter

Simultaneously with CBF, the gray matter volume data of all participants were obtained on the same MRI examinations. The parameters of three-dimensional sagittal T1-weighted magnetization-prepared rapid acquisition with gradient echo images were as follows: repetition time = 7.12 ms, echo time = 3.4 ms, matrix = 260×320, field of view = 260×240, flip angle = 10°, number of excitations = 1, 0.6-mm effective slice thickness with no gap, 300 slices. The scan time was 4 min and 1 s.

For volumetric confirmation of HS, we used FreeSurfer software (v.5.3, https://surfer.nmr.mgh.harvard.edu) to assess the hippocampal volumes based on the 3D T1-weighted images of all the participants. Image processing included the removal of nonbrain tissues with a hybrid watershed/surface deformation procedure, automated Talairach transformation, and segmentation of the subcortical structure and cortex. The obtained hippocampal volumes were expressed as the laterality index (LI) calculated as follows: (left side − right side) / (left side + right side). As a result, the LIs of the three groups were the following: healthy controls [mean ± SD = −0.012 ± 0.032; range = −0.066–0.034], patients with left TLE [mean ± SD = −0.208 ± 0.071; range = −0.339 to −0.093], and patients with right TLE [mean ± SD = 0.193 ± 0.073; range = 0.101–0.361]. Both patients with left and right TLE showed significantly lower and higher values, respectively, than healthy controls (one-way ANOVA and post hoc Tukey, both $p < 0.001$).

To complement the graph theory analyses, we compared gray matter estimates between groups using t-tests implemented in statistical parametric mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB after standard normalization of VBM8 (i.e., segmentation, spatial normalization by DARTEL, and smoothing with a 4-mm full-width at half-maximum Gaussian kernel). Finally, we created the T-value maps in each comparison using the cutoff T-values of the height threshold $p < 0.001$ (uncorrected).

2.4. Graph theoretical analysis

The graph theoretical analysis in this study was performed with the Graph Analysis Toolbox (GAT) software program [17]. Graph Analysis

Table 1
Demographics of the patients with left and right temporal lobe epilepsy (TLE) and the healthy subjects.

Feature	Left TLE (n = 19)	Right TLE (n = 21)	Controls (n = 20)	p-Value
Gender (no.)				
Men:Women	5:14	11:10	8:12	0.24 [*]
Age at examination (years)				
Mean ± SD	41.4 ± 12.5	46.5 ± 12.0	44.1 ± 12.0	0.46 [†]
Disease duration (years)				
Mean onset age ± SD	13.1 ± 9.8	16.2 ± 14.5	N/A	0.43 [‡]
Mean duration of epilepsy ± SD	28.3 ± 10.4	30.3 ± 14.6	N/A	0.62 [‡]
Current treatment (no.)				
Mean no. of AEDs ± SD	2.26 ± 1.10	2.76 ± 1.09	N/A	0.16 [‡]

AEDs: antiepileptic drugs, N/A: not available, [*]Pearson's χ^2 test, [†]one-way ANOVA, [‡]unpaired t-test.